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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,618	05/05/2006	Brenda F. Baker	CORE0005USA	9771

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
12/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,618	BAKER, BRENDA F.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,40 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,40 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/3/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim Rejections - 35 USC § 103

Claims 38, 40 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (US 2004/0192626, of record) in view of Brown et al. (US 2003/0166282, of record).

The claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises 2'-fluoro nucleosides and all guanosines have been substituted with inosine in the sense strand. In specific embodiments the compounds are 12-30 or 19-23 nucleotides in length.

McSwiggen et al. teach siRNAs that are about 19 to about 25 nucleotides in length and comprise an antisense region complementary to a sequence encoding a target RNA and a sense region complementary to the antisense region. McSwiggen et al. teach the use of chemically modified siRNAs, with chemical modifications including 2'-deoxy-2'-fluoro ribonucleotides, which improve the stability of the interaction with the target RNA sequence and to improve nuclease resistance. At paragraph 15 McSwiggen et al. teach that up to 100% of the nucleotide positions within an siRNA can be modified. Figure 18 illustrates embodiments wherein all nucleotide positions of the antisense strand comprise 2'-modified sugars. This figure is present in provisional

application 60/408,378, filed September 5, 2002. McSwiggen et al. additionally teach that "universal bases" may be included in a siRNA, teaching at paragraph 209 that inosine is an example of a universal base. McSwiggen et al. teach modifications to nucleotides in a permissive manner, but does not explicitly teach a siRNA wherein every position of the antisense strand contains a 2'-fluoro modified nucleotide and every guanosine in the sense strand is substituted with inosine.

Brown et al. teach siRNAs comprising modified nucleotides that have the effect of decreasing the duplex stability of the dsRNA. Brown et al. teach at paragraph 29 that such siRNAs are significantly more potent. At paragraph 33 Brown et al. teach that because I:C base pairs form only two hydrogen bonds instead of the three in G:C base-pairs, substitution of inosine (I) for G at one or more positions in the siRNA will reduce duplex stability and thereby enhance siRNA potency. At paragraph 196 Brown et al. teach that inosine can be substituted for guanosine in any siRNA sequence by using an appropriate inosine phosphoramidite.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs comprising a completely modified antisense strand as taught by McSwiggen et al. and to make this siRNA with all fluoro modifications because McSwiggen et al. teach siRNAs wherein all positions of the antisense strand comprise 2'-modified sugars and explicitly teach the inclusion of 2'-fluoro nucleotides. Based on these teachings and the permissive manner in which McSwiggen et al. teach the inclusion of 2'-modified nucleotides and the knowledge that such nucleotides can be incorporated into an oligomer using commercially available reagents and routine

synthetic methods, one of ordinary skill in the art would recognize that making the siRNA with all fluoro nucleotides instead of mixed 2'-fluoro and 2'-OMe nucleotides is a matter of design choice. It would also have been obvious to make an siRNA with one or more inosine bases that will reduce duplex stability as taught by Brown et al. Brown et al. provide a motivation to include inosine nucleotides in a siRNA by teaching that use of such an analog will reduce duplex stability and increase potency of the siRNA and provides a reasonable expectation of success in making siRNAs comprising inosine by teaching that inosine can be easily substituted for guanosine using an appropriate phosphoramidite. Based on the suggestion by Brown et al. of including inosine nucleotides in a siRNA and their teaching that such nucleosides are easily substituted for guanosine using routine synthetic methods and readily available reagents, one of ordinary skill in the art would recognize that placement of the inosine at any particular position, including the 3' terminus of the sense strand, is a matter of design choice that would be made in the course of routine optimization.

Thus, the invention of claims 38, 40 and 61 would have been obvious, as a whole, at the time the invention was made.

Claims 38, 40 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al. (US 2004/0192626, of record) in view of Zamore et al. (US 2005/0181382, of record).

The claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises 2'-fluoro

nucleosides and all guanosines have been substituted with inosine in the sense strand. In specific embodiments the compounds are 12-30 or 19-23 nucleotides in length.

McSwiggen et al. teach siRNAs that are about 19 to about 25 nucleotides in length and comprise an antisense region complementary to a sequence encoding a target RNA and a sense region complementary to the antisense region. McSwiggen et al. teach the use of chemically modified siRNAs, with chemical modifications including 2'-deoxy-2'-fluoro ribonucleotides, which improve the stability of the interaction with the target RNA sequence and to improve nuclease resistance. At paragraph 15 McSwiggen et al. teach that up to 100% of the nucleotide positions within an siRNA can be modified. Figure 18 illustrates embodiments wherein all nucleotide positions of the antisense strand comprise 2'-modified sugars. This figure is present in provisional application 60/408,378, filed September 5, 2002. McSwiggen et al. additionally teach that "universal bases" may be included in a siRNA, teaching at paragraph 209 that inosine is an example of a universal base. McSwiggen et al. teach modifications to nucleotides in a permissive manner, but does not explicitly teach a siRNA wherein every position of the antisense strand contains a 2'-fluoro modified nucleotide and every guanosine in the sense strand is substituted with inosine.

Zamore et al. teach asymmetric siRNAs that provide enhanced specificity and efficacy for mediating RISC-mediated cleavage of a desired target gene. These siRNAs are described at paragraphs 80-82. In one preferred aspect the base pair strength between the antisense strand 5' end and the sense strand 3' end of the siRNAs is less than the bond strength or base pair strength between the antisense strand 3' end and

the sense strand 5' end, such that the antisense strand preferentially guides cleavage of a target mRNA. In one embodiment, the bond strength or base pair strength is less due to at least one base pair comprising a rare nucleotide such as inosine (I). These teachings are present in the provisional application filed June 2, 2003.

Zamore et al. demonstrate this concept in example IV, producing siRNAs having I:C base pairs at the 5' terminus of the antisense strand. When the 5' terminus of the anti-sense strand is substituted with inosine the anti-sense strand was enhanced relative to the sense strand. Thus, the strand whose 5' end is in the weaker base pair was more effective at target cleavage.

At paragraphs 89-92 Zamore et al. further teach that the siRNAs can be modified to improve stability in serum or in growth medium for cell cultures. Preferred nucleotide analogues include sugar-modified ribonucleotides where the 2'OH-group is replaced by groups such as halo, which includes fluorine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs comprising a completely modified antisense strand as taught by McSwiggen et al. and to make this siRNA with all fluoro modifications because McSwiggen et al. teach siRNAs wherein all positions of the antisense strand comprise 2'-modified sugars and explicitly teach the inclusion of 2'-fluoro nucleotides. Based on these teachings and the permissive manner in which McSwiggen et al. teach the inclusion of 2'-modified nucleotides and the knowledge that such nucleotides can be incorporated into an oligomer using commercially available reagents and routine synthetic methods, one of ordinary skill in the art would recognize that making the

siRNA with all fluoro nucleotides instead of mixed 2'-fluoro and 2'-OMe nucleotides is a matter of design choice. It would also have been obvious to make an siRNA with an inosine base that will produce asymmetry within the siRNA as taught by Zamore et al. Zamore et al. provide a motivation and reasonable expectation of success in including inosine nucleotides in a siRNA by teaching and exemplifying that inclusion of such a nucleoside reduces the base pairing strength and provides a motivation to reduce the base pair strength between the antisense 5' end and the sense 3' end by teaching that reducing strength of this particular base pair enhances cleavage of the target mRNA. While Zamore et al. exemplify the use of inosine in the antisense strand and not the sense strand, one of ordinary skill in the art would recognize that reversing the I:C base pair to place the inosine in the sense strand produces an equivalent structure that is also an asymmetric siRNA having an enhanced antisense strand.

Thus, the invention of claims 38, 40 and 61 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants argue the McSwiggen reference describes siRNA molecules targeted to the IKK-gamma and PKR genes, broadly discusses possible modification and describes active siRNA molecules with chemical modifications that differ from the claimed oligonucleotides. Applicants note that none of these specific molecules have an antisense strand in which each nucleoside comprises a 2'-fluoro modification and a sense strand wherein each guanine is substituted with an inosine.

It is correct that the working examples of McSwiggen are not directed to the particular limitations of the instant claims, but the disclosure of the prior art is not limited to exemplified or preferred embodiments. McSwiggen explicitly contemplates the use of 2'-fluoro modifications and teaches siRNAs wherein every position comprises a 2' modification. It is also correct that McSwiggen does not exemplify an siRNA having the exact limitations of the instant claims; however an obviousness rejection does not require that all limitations be found in any one reference. McSwiggen teaches full 2' modification of the antisense strand and explicitly contemplates inclusion of inosine bases in an siRNA.

Applicants argue the Brown and Zamore references do not suggest that use of inosine would be any more advantageous or desirable than any of the other chemical modifications contemplated and provides no guidance regarding which position or strand should be modified. Applicants further note neither Brown nor Zamore describe introducing 2'-fluoro groups into each nucleoside of the antisense strand of siRNA molecules.

These arguments are not persuasive because a teaching that inosine would be the most advantageous or desirable modification is not required; while Brown does contemplate other modifications, the reference nevertheless also provides an explicit reason to use inosine and provides guidance of what position to modify by suggest its use as a replacement for guanosine. Applicants argue that the Zamore reference provides no specific guidance regarding the number and placement of modified

nucleosides within siRNA duplexes; however the examiner notes that this reference is not relied upon for such teachings, which are found in the McSwiggen reference. It is correct that neither Brown nor Zamore describe an antisense strand fully modified with 2' fluoro nucleotides, however the instant rejection is for obviousness, which does not require all claim limitations be found in a single reference.

Applicants argue the combined teachings of McSwiggen and Brown or McSwiggen and Zamore indicate a vast number of chemical modifications that can be introduced at every possible position in an siRNA, resulting in a nearly limitless combination of possible modifications.

This argument appears to be stating that the cited art does not suggest the claimed combination of modifications with sufficient specificity. However, the rejection sets forth how each modification is individually suggested in the references and why each would be chosen by one of ordinary skill in the art in order to obtain a desired characteristic.

Applicants argue the art of siRNA design at the time of the invention was unpredictable and one of ordinary skill could not have anticipated which chemical modifications in siRNA duplexes would have resulted in active compounds.

While it is correct one cannot predict activity *a priori*, the examiner notes that the instant claims do not require any degree of activity. Furthermore, an obviousness rejection requires only a reasonable expectation of success. In the instant case, each of the individual references suggests the claimed modifications and exemplifies their

use, providing a reasonable expectation that these modifications in combination will result in an active siRNA.

Applicants argue that the claimed compounds mirror the situation in the recent decision in *Takeda* and in view of the unpredictability in the art of siRNA design and production the claimed invention is not obvious.

The arguments regarding *Takeda* are not persuasive because the fact pattern in Takeda is not the same as in the instant application. The relevant question in *Takeda* was the obviousness of taking a known lead compound and converting it to another, different compound. However, the instant claims are not directed to a lead compound and the rejection is not based on changing a known compound to a completely new compound.

Applicants argue that improving any one property may reduce or abolish another property and that balancing competing properties has proven to be unpredictable and extremely challenging. Applicants conclude that when one considers the state of the art on balance, it is clear the modifications described in the cited references are neither universally beneficial nor detrimental.

These arguments are not persuasive because a rejection based on obviousness does not require that a modification be universally beneficial, only that one have a reasonable expectation of success in making the compound. Although no data has been provided to support the assertion regarding the difficulties of balancing competing properties, as noted above the claimed compounds are not required to have activity; therefore a balance of different properties is not required.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5.

The examiner is currently the acting supervisor for art unit 1635. The central FAX Number is 571-273-8300.

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